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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
SITTON, JEHANNE SOUAYA	
ART UNIT	**PAPER NUMBER**
1634	

NOTIFICATION DATE	DELIVERY MODE
10/03/2007	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patentadministrator@clarkelbing.com

Office Action Summary	Application No.	Applicant(s)	
	10/656,873	FISHMAN ET AL.	
	Examiner	Art Unit	
	Jehanne S. Sitton	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 July 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,6 and 8-32* is/are pending in the application.

4a) Of the above claim(s) *8-19* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,6 and 20-32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 7/17/2007 has been entered.

2. Currently, claims 1-3, 6, and 8-32 are pending in the instant application. Claims 8-19 are withdrawn from consideration as being drawn to non elected inventions. Claims 1-3, 6, and 20-32 are currently under examination. All the amendments and arguments have been thoroughly reviewed but are deemed insufficient to place this application in condition for allowance. The following rejections are either newly applied, as necessitated by amendment, or are reiterated. They constitute the complete set being presently applied to the instant Application. Response to Applicant's arguments follow. This action is Non-FINAL.

3. The New Matter rejection made in the previous office action is withdrawn in view of the amendments to the claims to recite "has an increased likelihood" and to delete "may have or be at risk".

Claim Rejections - 35 USC § 112

4. Claims 1-3, 6, and 30-32 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not

described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. There are many factors to be considered when determining whether there is sufficient evidence to support determination that a disclosure does not satisfy the enablement requirements and whether any necessary experimentation is undue. These factors have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention and the breadth of the claims:

The claims are broadly drawn to a method for determining whether a human test subject has, is at risk of developing, or has an increased likelihood of *any* titin related disease or condition of the heart by detecting *any* mutation from a titin gene, including a naturally occurring gene. The claims are further drawn to a method of determining whether any test subject, including mammals and humans, has an increased likelihood of a titin related disease or condition of the heart or facilitating the etiology of an existing heart disease or condition by detecting *any* mutation from a titin gene, from any source. The claims are further limited to heart failure as well as any mutation in a cardiac specific exon as well as the N2B exon of titin.

The nature of the invention, therefore, requires the knowledge of predictive associations between any mutation in a titin gene from any subject, including humans and any condition or disease of the heart.

The amount of direction or guidance and presence and absence of working examples:

The specification teaches that heart disease is a general term used to describe different heart conditions. The specification teaches that risk factors include coronary artery disease, hypertension, valvular heart disease, cardiomyopathy, disease of the heart muscle, obesity, diabetes, and family history of heart failure (see page 1). The specification teaches that during a mutation screening of zebra fish, a phenotype resulting from mutation of the titin gene was observed which was similar to mammalian heart failure (page 1).

The specification teaches that the claimed recitation of a "titin gene" is drawn to a nucleic acid that encodes a titin protein or polypeptide that has 45%, 60%, 75% and 90% identity to the sequence of human or zebra fish titin molecules (see p. 3). Such a recitation encompasses mutants, allelic variants, and homologs of titin from any source, which have not been taught or described in the specification. The specification further defines "titin related disease or condition" to mean a disease or condition that results from an inappropriately high or low expression of a titin gene or a mutation in a titin gene that alters the biological activity of a titin nucleic acid or polypeptide. Therefore, the recitation encompasses any substitution, deletion or insertion in any titin gene. The specification teaches that the methods include diagnostic assessment of heart disease, heart failure (page 8, first full para), congestive heart failure, and coronary artery diseases or conditions associated with valve formation defects (page 9). The specification, however, has only taught a single mutation in the N2B exon of titin that was found in zebra fish embryos characterized with a weak heartbeat (see p. 20). Further, the whereabouts of this mutation in the N2B exon are unclear as the specification only teaches that identification of a T-G transition in the *pikm171* allele was found which resulted in a change of leucine in the

IS3 fragment of N2B domain into a stop codon. The specification, however, does not teach at which leucine residue this mutation occurs. In addition, the specification does not define the specific genotype of the *pickwick* mutation. The specification recites "a mutation in a cardiac specific exon, such as the N2B exon, e.g. the *pickwick* mutation" (see p. 2, lines 9-10), thus it is unclear from this recitation or the teachings in the specification as to what is encompassed by the *pickwick* mutation. Xu (Xu et al; Nature Genetics, vol. 30, pages 205-209; 2002) teaches that there are multiple alleles in the *pik* complementation group (see abstract), however the specification provides no description of the other alleles. The specification has only taught a single mutation that appears to be associated with a weak heart beat in zebra fish embryos, but the specific genotype of this mutation is not taught.

The specification has not taught any working examples of any other mutations in the titin gene from zebra fish, or any other species including any mammals or human population, which is associated with a titin related disease or condition of the heart. Further, the specification has not taught an association between the pickwick mutation and any of the diseases or conditions which is encompassed by the claims, in zebra fish or in any other species, including mammals. Although the specification teaches that the pickwick mutation is associated with a weak heartbeat in zebra fish, which may be similar to mammalian heart failure, such is not necessarily diagnostic of mammalian heart failure, let alone any disease or condition of the heart in any mammal or human. While a weak heart beat may lead to heart failure, there are other causes for heart failure including coronary artery disease, hypertension and diabetes (as taught by the specification at page 1). Therefore, while coronary artery disease, hypertension, or diabetes may all lead to heart failure, a mutation which is associated with any one of these disease or

conditions is not necessarily *diagnostic* of another. Each represents a specific disease which have different symptoms and causes. The specification has not established a universal correlation between any mutation in any titin gene and an association with any disease or condition of the heart as is broadly claimed.

The specification does not teach or provide any guidance as to which regions or amino acids in the titin gene would be affected to provide for the diagnostics or associations set forth in the claims. The specification does not teach or provide any guidance as to what information one of skill in the art would conclude, as to the etiology of an existing heart disease or condition, from the fact that a subject possessed any mutation in a titin gene. The specification teaches a single phenotype, the pickwick mutation, but does not teach what this position is in the titin gene from zebra fish or any other species, nor does it teach if the T to G transversion even exists in other species. The specification does not teach what other positions within the titin gene of zebra fish or the titin gene from other species would provide the same phenotype or whether a polymorphism or mutation would have the same effect in another gene. The specification provides no guidance as to conserved and nonconserved positions in titin from different species. The specification provides no guidance regarding which specific amino acids, domains, or regions within titin would be "informative" nor what disease etiology they would be "informative" for.

The state of the prior art and the predictability or unpredictability of the art:

While the claims are broadly drawn to detecting any mutation in any region of the titin gene and association to any disease or condition of the heart, Garvey (Garvey et al; Genomics,

vol. 79, pages 146-149, 2002) teaches that titin is differentially spliced with a cardiac muscle isoform N2B and a skeletal muscle isoform N2A (see page 146, col. 2). Garvey teaches a mutation in mouse titin which disrupts the N2A domain but which was not associated with any cardiac muscle pathology. Accordingly, it is clear that a mutation or polymorphism in "any region" of titin is not universally correlative of an association with heart disease. This lack of universal association is also true of the cardiac isoform of human titin. For example, Itoh-Satoh et al (Biochemical and Biophysical Research Communications, vol. 291, pp 385-393; 2002) teach a mutation in the titin gene which may be associated with Dilated Cardiomyopathy (p. 387, col. 2, lines 7-13), but another mutation, Arg328Cys, was found in healthy control subjects, indicating that it is a polymorphism not related with DCM (col. 2, lines 3-5). Additionally, Siu (Siu et al; Circulation, March 1999, vol. 99, pages 1022-1026) teaches that five variations were found in the N2B region of human titin, including 3 which did not alter the protein sequence and 2 which did, but that were determined to not be disease-causing mutations (page 1025, col. 2).

The prior art provides no analysis of mutations in titin and comparisons to similar positions across species. The prior art does not provide any analysis of titin function with regard to mutational analysis nor does it provide any indication of mutations in regions of titin which would be associated with heart disease or conditions. The post filing date art of Itoh-Satoh teaches a number of mutations in human titin, but also provides alignments across different species. As seen in figures 1 and 2, the amino acid positions are not necessarily conserved across different species, especially noting the differences found in the Z line region between chicken and human titin sequences.

The level of skill in the art:

The level of skill in the art is deemed to be high.

The quantity of experimentation necessary:

The teachings of the specification are insufficient to provide one of skill in the art with a predictable correlation that any substitution, deletion or insertion in the titin gene, or more specifically the IS3 fragment of N2B would result in a weak heartbeat in zebra fish embryos or any other species. The single point mutation set forth in the specification, whose location is not taught, also does not provide one of skill in the art with a predictable correlation as to an association between any mutations in any titin gene from any source, including humans, and any disease or condition of the heart, including heart failure. The specification lacks sufficient guidance to enable one of skill in the art to make or use the invention as broadly as it is claimed, without undue experimentation.

To practice the invention as broadly as it is claimed the skilled artisan would have perform an enormous amount of research to determine the enabled scope of the claims. For example, the skilled artisan may be required to mutate each position of the titin gene from each species, which encodes a protein which is on the order of 27,000 amino acids, and perform functional analysis to determine which positions and what alterations are associated with diseases or conditions of the heart, as well as which positions would be informative regarding etiology of a disease or condition of the heart. Alternatively, or in addition, the skilled artisan would be required to perform a large study which included subjects affected with a large number of different diseases or conditions of the heart as well as controls and to screen such for any

mutation in a titin gene to determine which mutations were predictably correlative of disease and which were not, as well as what information they would be able to provide. Such analysis would consist of unpredictable trial and error research projects as evidenced by the art cited above. An enormous amount of inventive effort would be required for these research projects, with each intervening step not being predictive of any particular outcome. For example, given the lack of guidance in the specification and the art, the skilled artisan would not have been able to predict the mutations taught by Itoh-Satoh nor would the skilled artisan have been able to distinguish which of the mutations taught by Siu and Itoh-Satoh are associated with disease as opposed to those that are not.

It is known for nucleic acids as well as proteins that a single nucleotide or amino acid change or mutation can alter the function of the biomolecule in some instances. Given the lack of guidance in the art at the time the invention was made as well as the lack of guidance in the specification, the effects of these changes are unpredictable as to which ones have a significant effect versus not. The specification has not provided the skilled artisan with any teaching or guidance as to which nucleotide or amino acid positions in the titin gene would be responsible for normal or aberrant activity of the titin protein. Without such, the skilled artisan would further be unable to predictably correlate which mutations would have and would not have an effect on the function or activity of any titin protein. The art exemplifies this unpredictability.

Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the large quantity of research required to define these unpredictable variables, the lack of guidance provided in the specification, the absence of a working example and the negative teachings in the prior art balanced only against the high skill level in the art, it is

the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as broadly written.

Response to Arguments

5. The response traverses the rejection. The response asserts that claim 1has been amended to specify a "naturally occurring human titin gene". The amendment and argument have been thoroughly reviewed but were not found persuasive to overcome the rejection. The term "titin gene" as defined by the specification, encompasses mutants, allelic variants, and homologs of titin, in humans. Further, claim 23 is not limited to a human titin gene, and thus encompass mutants, allelic variants and homologs from "any source" including any species, which is still an extremely large number of possible allelic variants, mutants, and homologs of any titin gene as well as the human titin gene, which is encompassed by the amended claims and does not narrow the scope of the claims to overcome the rejection. The specification has provided no guidance for the skilled artisan to predictably determine which mutations in titin, including human titin, are associated with a disease or condition of the heart or which facilitate the etiology of an existing heart condition, from those that are not associated. The fact that claim 1 recites "naturally occurring human titin gene" does not overcome this.

The response further asserts at page 9 and 11, that detection of a mutation in a titin gene "may certainly" provide information as to whether it is possible that the mutation may be related to the etiology of a disease or condition of the heart. The response asserts that if there is no such mutation, then the protein does not likely play a role in the disease or condition and if there is a mutation, it is reasonable to conclude that it may possibly play a role in the disease or condition. The response also asserts that even if a particular mutation is determined to not play a role in

disease, the detection of the mutation indicates a possibility that a medical professional may wish to have knowledge of and evaluate. The response asserts that because titin plays an important role in proper heart function, the presence of mutations in titin sequences (or not) provides valuable information. The response also asserts that the claims do not require a definitive diagnosis every time, but could be used in conjunction with other tests to arrive at a diagnosis. These arguments have been thoroughly reviewed but were not found persuasive. Firstly, the fact that a mutation is not present does not necessarily indicate that the protein "does not likely play a role in the diseases or condition" because mutations are not the only link between proteins and disease, for example aberrant expression may play a role. However, the specification provides no guidance on this. Additionally, the presence of a mutation would not appear to lead the skilled artisan to reasonably conclude that titin may possible play a role in the disease or condition as evidenced by the teachings in the art as to mutations in titin which are NOT associated with a titin-related disease or condition of the heart. Further, the response does not provide any indication as to what information would be useful to a health professional regarding a titin mutation, if the health professional would have no way to predictably know whether the mutation was in fact associated with a disease or condition of the heart. As evidenced by the art cited above, the mere fact that a mutation may exist in the titin gene does not necessarily provide any information as to the etiology, that is the cause of the disease, or even whether the mutation may play a role in a disease or condition of the heart, or whether the mutation is important for proper heart function because mutations in titin are not necessarily associated with disease, as evidenced by the cited art, nor would they necessarily affect heart function. Since the specification provides no guidance as to which mutations are associated with disease or those

that alter heart function or titin function, vs those that are not associated or do not alter heart function or titin function, the experimentation required to practice the broad scope of the claimed invention is in fact a research project, which requires extensive unpredictable trial and error experimentation to actually determine what the enabled scope of the claims are.

The response asserts although Itoh-Satoh may indicate that the matter is complex, it is clear that mutations in titin play a role in cardiomyopathy, and that the fact that some mutations in titin may not play a role in disease does not negate the fact that other titin mutations may have such roles. The response asserts that as Applicants have shown that titin plays a role in heart function, the analysis of mutations would appear to be an important step in characterizing a heart condition. The response then asserts that with regard to the Siu reference, teaching of a particular diagnostic mutation is not required as those of skill in the art can readily analyze sequences from many people to determine which mutations may correlate with disease without undue experimentation. These arguments have been thoroughly reviewed but was not found persuasive as the claims specifically set forth that the mere detection of a mutation is an indication that a test subject has, is at risk of developing, has an increased likelihood of a titin-related disease or condition of the heart or provides information as to the cause (etiology) of an existing heart disease or condition, which is unpredictable. The claims do not appear to be drawn to methods of analyzing mutations to determine which are associated nor to methods of screening a population of people to determine which mutations correlate with disease, as these steps are not recited. Regardless of the availability of sophisticated sequencing techniques, without further guidance from the specification, these techniques provide no teaching of which mutations are disease or functionally associated vs those that are not. Sequencing is merely a

tool that the skilled artisan would use to determine the enabled scope of the invention, not an actual teaching of which mutations are disease associated vs not.

The response asserts that they are not claiming methods for all possible causes of heart failure, rather claim 1, from which claim 6 depends, specifies that the subject disease or condition is titin related, thus if a disease or condition is not related to titin, then it is not part of the present claims. This argument has been thoroughly reviewed but was not found persuasive as the claims do encompass any disease or condition of the heart, including heart failure. The only mutation taught in the specification is a mutation in zebrafish which causes a weak heartbeat. However, the claims are more broadly drawn to any "disease or condition of the heart" which encompasses a large number of diseases or conditions which are not necessarily a result of a weak heartbeat. For example, although the phenotype of the zebrafish, that is a weak heartbeat, may be similar to mammalian heart failure, such is not necessarily diagnostic of mammalian heart failure, let alone any disease or condition of the heart. Further, the specification has provided no guidance as to which mutations in the human titin gene would be cause a weak heartbeat, heart failure, or any other disease or condition of the heart, let alone any other mammalian titin gene, or what mutations in the zebrafish titin gene would have the same phenotype.

The response asserts that the teachings of Itoh Satoh confirm that the experimentation required is not undue, and that the experiments of Itoh-Satoh do not negate the fact that detection of mutations in the titin gene can be correlated with diseases or conditions of the heart without undue experimentation because "it was simple" for Itoh Satoh to determine the relevance of this mutation. This argument has been thoroughly reviewed but was not found persuasive. The

teachings of Itoh-Satoh exemplify that associating any mutation in the titin gene with any disease or condition of the heart, risk of disease or condition, as well as facilitating the etiology of any disease or condition of the heart, is unpredictable (Itoh-Satoh teaches that a mutation exists in the titin gene which results in an altered titin protein sequence and that such is not associated with dilated cardiomyopathy, a disease or condition of the heart), without actually conducting a population study to determine whether any particular mutation is disease associated. The examiner is not stating that a screening assay such as a population based study with control samples is necessarily difficult. Further these arguments are confusing because the claims are not directed to a screening assay, rather the claims specifically set forth that the mere detection of any mutation in any titin gene, from humans, mammals, as well as other sources, is indicative that a subject has, is at risk for, or has an increased likelihood of a titin related disease or condition of the heart, or provides information as to the etiology of an existing heart condition or disease. However, the specification provides no guidance as to which mutations are disease associated vs not. This does not require an absolute diagnosis, however, however the broad scope of the claims requires that there be some teaching or guidance as to which mutations would be disease associated vs not. It is this area in which the specification is deficient. Accordingly, the mere detection of a mutation, which is all that the claims require, would not provide the skilled artisan with any information as to an association of that mutation with a disease or condition of the heart. Case law has established that "(t)o be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.'" *In re Wright* 990 F.2d 1557, 1561. *In re Fisher*, F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) it was determined that "(t)he scope of

the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art". The amount of guidance needed to enable the invention is related to the amount of knowledge in the art as well as the unpredictability in the art. For these reasons and the reasons made of record in previous office actions, the rejection is maintained.

Written Description

6. Claims 1-3, 6, and 20-32 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are broadly drawn to a method for determining whether a human test subject has, is at risk of developing, or has an increased likelihood of *any* titin related disease or condition of the heart by detecting *any* mutation from a titin gene, including a naturally occurring gene. The claims are further drawn to a method of determining whether any test subject, including mammals and humans, has an increased likelihood of a titin related disease or condition of the heart or facilitating the etiology of an existing heart disease or condition by detecting *any* mutation from a titin gene, from any source. The claims are further limited to heart failure as well as any mutation in a cardiac specific exon as well as the N2B exon of titin.

The specification teaches that a during a mutation screening of zebra fish, a phenotype resulting from mutation of the titin gene was observed which was similar to mammalian heart

failure (page 1). The specification teaches that the claimed recitation of a "titin gene" is drawn to a nucleic acid that encodes a titin protein or polypeptide that has 45%, 60%, 75% and 90% identity to the sequence of human or zebra fish titin molecules (see p. 3). Such a recitation encompasses mutants, allelic variants, and homologs of titin from any source, which have not been taught or described in the specification. The specification further defines "titin related disease or condition" to mean a disease or condition that results from an inappropriately high or low expression of a titin gene or a mutation in a titin gene that alters the biological activity of a titin nucleic acid or polypeptide. Therefore, the recitation encompasses any substitution, deletion or insertion in any titin gene. The specification asserts that the methods include diagnostic assessment of heart disease, heart failure (page 8, first full para), congestive heart failure, and coronary artery diseases or conditions associated with valve formation defects (page 9). The specification, however, has only taught a single mutation in the N2B exon of titin that was found in zebra fish embryos characterized with a weak heartbeat (see p. 20). Further, the whereabouts of this mutation in the N2B exon are unclear as the specification only teaches that identification of a T-G transition in the *pikm171* allele was found which resulted in a change of leucine in the IS3 fragment of N2B domain into a stop codon. The specification, however, does not teach at which leucine residue this mutation occurs. In addition, the specification does not define the specific genotype of the *pickwick* mutation. The specification recites "a mutation in a cardiac specific exon, such as the N2B exon, e.g. the *pickwick* mutation" (see p. 2, lines 9-10), thus it is unclear from this recitation or the teachings in the specification as to what is encompassed by the *pickwick* mutation. Xu (Xu et al; Nature Genetics, vol. 30, pages 205-209; 2002) teaches that there are multiple alleles in the *pik* complementation group (see abstract),

however the specification provides no description of the other alleles. This recitation, therefore, appears to encompass any mutation with the *pickwick* phenotype (p. 19, lines 4-5). The specification, however, has only taught a single mutation that appears to be associated with a weak heart beat in zebra fish embryos, but the specific genotype of this mutation is not taught.

The specification provides insufficient written description to support the genus of titin genes or mutations encompassed by the claims. The claims encompass a large genus of nucleic acids which comprise mutations in any region of a titin gene from any species. The genus includes an enormous number of polymorphisms and mutations for which no written description is provided in the specification. For example, the art of Itoh-Satoh provides for mutations which have not been taught or described in the specification in any way. The large genus encompassed by the claimed is represented in the specification by only the generally described single mutation which is associated with the "pickwick" phenotype. The specification does not teach the specific location of this mutation in the titin gene from zebra fish nor does it teach what a corresponding position would be in any other species. Thus, applicant has express possession of only a single undefined mutation in a genus which comprises hundreds of millions of different possibilities. Here, no common element or attributes of the sequences are disclosed which would permit selection of sequences as polymorphisms or mutations. No structural limitations or requirements which provide guidance on the identification of sequences which meet these functional limitations of associating a polymorphism with any disease or condition of the heart.

Further, these claims expressly encompass allelic variants including insertions, deletion, substitutions and transversions at thousands of different sites. However, no predictable correlation between the structural alterations of the single polymorphism and the functional

association to heart disease is provided by the specification. Therefore, the skilled artisan would be unable to predictably correlate any other structural change in any other region of titin from "any" species and an association with any disease or condition of the heart as is broadly claimed.

The specification provides no correlation between the structure of mutations in titin and the function of such mutations with diseases or conditions of the heart. The mutation shown is not representative of the enormous genus of structurally and functionally distinct mutations which would be associated with the large number of different diseases and conditions of the heart because it is not known which mutations would have the same affect.

In analysis of the claims for compliance with the written description requirement of 35 U.S.C. 112, first paragraph, the written description guidelines note regarding genus/species situations that "Satisfactory disclosure of a ``representative number" depends on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed." (See: Federal Register: December 21, 1999 (Volume 64, Number 244), revised guidelines for written description.) In the instant case, the specification fails to teach the necessary common attributes or features of the genus of encompassed nucleic acids and mutations in view of the single species disclosed. As such, one of skill in the art would not recognize that applicant was in possession of the genus of nucleic acids and polymorphisms encompassed by the broadly claimed invention.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry,

whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.)

The skilled artisan cannot envision the detailed chemical structure of the encompassed nucleic acids and mutations, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. The nucleic acid itself is required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993), and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. The current situation is a definition of the compound solely based on its functional utility, as a polymorphism, without any definition of the particular polymorphisms claimed.

Finally, University of California v. Eli Lilly and Co., 43 USPQ2d 1398, 1404, 1405 held that:

To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); In re Gosteli, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) (" [T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." Lockwood, 107 F.3d at 1572, 41 USPQ2d at 1966.

An adequate written description of a DNA, such as the cDNA of the recombinant plasmids and microorganisms of the '525 patent, "requires a precise definition, such as by structure, formula, chemical name, or physical properties," not a mere wish or plan for obtaining the claimed chemical invention. Fiers v. Revel, 984 F.2d 1164, 1171, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993). Accordingly, "an adequate written description of a DNA requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it; what is required is a description of the DNA itself." Id. at 1170, 25 USPQ2d at 1606.

Response to Arguments

7. The response traverses the rejection and asserts that claim 1 has been amended to specify a "human" gene. This argument has been thoroughly reviewed but was not found persuasive as

the specification has provided no written description of any mutations in the human titin gene. The single mutation in zebrafish, taught in the specification, is not representative of the enormous genus of functionally associated mutations encompassed the by the claims as the specification does not teach what this specific mutation is, nor does it provide a structure function correlation between the mutation in zebrafish and any other members of the genus.

The response further asserts that it is not necessary to have described additional particular mutations as a reference sequence to compare a test sequence to has been provided, and those skilled in the art could readily determine whether a test sequence differs from the reference, without undue experimentation. This argument has been thoroughly reviewed but was not found persuasive as the claims are rejected under the written description portion of 112/first paragraph. In meeting the written description requirement of 112/first paragraph, the written description guidelines note regarding genus/species situations that "Satisfactory disclosure of a ``representative number'' depends on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed." The claims are drawn to and encompass the fact that the detection of any mutation in titin will provide a functional association with heart disease. However, as exemplified by the art cited, not all mutations in titin are disease associated. However, the specification provides no guidance as to the necessary common attributes of features of heart disease associated mutations. The teachings of the wildtype human titin gene does not provide any guidance or description as to which mutations are disease associated vs those that are not. While the specification provides general description of how to detect mutations in known sequences, the *claims* are drawn to detecting a large number

of possible undescribed diagnostic mutations (for any disease or condition of the heart) in a large number of undisclosed and undescribed titin genes, variants, and homologs, in any species. The rejection does not require that every possible mutation that could be associated with these diseases, or that every possible titin sequence, be identified or disclosed. Rather, the rejection stated that "[the mutation taught in the specification] is not representative of the large number of substitutions, deletions, and insertions in any [naturally occurring] titin gene from any source, including humans, that are encompassed by the claimed invention." It is further noted that claims 23-32 are not limited to human sequences. For these reasons and the reasons already made of record, the rejection is maintained.

Claim Rejections - 35 USC § 102

8. Claims 1-3, 6, 20, 21, and 23-31 are rejected under 35 U.S.C. 102(a) as being anticipated by Satoh et al (Biochemical and Biophysical Research Communications, vol. 262, pp 411-417, 1999).

With regard to claims 1, 4-6, 20, 21, 23-25, and 28-31, Satoh teaches of an A to T transversion in codon 740 of the titin gene of a human patient with hypertrophic cardiomyopathy, which replaces an Arginine with Leucine (see abstract). Satoh teaches that this mutation was not found in more than 500 normal chromosomes (see abstract). With regard to claims 2, 3, 26 and 27, Satoh teaches that genomic DNA was extracted from each subject and that PCR primers flanking each exon of the titin gene were designed to amplify each exon (p. 412-col. 1, "PCR-DCP analysis") and that to identify the mutation in exon 14, the PCR product was cloned into a vector and sequenced (para. bridging cols 1 and 2, p. 412).

Response to Arguments

9. The response requests that the rejection be withdrawn in view of an accompanying Declaration by inventor Xialei Xu, which was submitted in the parent application. The response asserts that applicants established a connection between a mutation causing a weak heartbeat in the titin gene and thus reduced the invention to practice, prior to the publication date of the Satoh reference. This argument, as well as the declaration, have been thoroughly reviewed but were not sufficient to overcome the rejection for the following reasons:

A) The declaration does not contain an allegation that the acts relied upon to establish the date prior to the reference were carried out in this country or in a NAFTA country or WTO member country (see MPEP 715.07(c)).

B) The declaration is only executed by one inventor, however it is unclear whether both inventors invented the subject matter in the claims or which inventor invented the subject matter in each claim (for example, paragraph 2 of the declaration states "my co-inventor and I").

C) The declaration and the exhibit have been thoroughly reviewed but are not sufficient to overcome the rejection. Firstly, it is noted that the exhibit was difficult to read and follow in places and that an explanation of relevant steps was not provided in the declaration. With regard to broad scope of the claims, as well as to the specific species encompassed by claims 1-3, 6, 20-2, 28-29, for example, neither the statement in the declaration (para 2) nor the exhibit exemplify actual or constructive, conception or reduction to practice, of 1) a method to determine whether *a mammal or a human* (claims 1-3, 6 and 20-22, and encompassed by clams 23-32 and specifically recited in claims 28-29) is at risk of developing a titin related disease or condition of the heart by determining whether *a mammal or a human* has a mutation in a naturally occurring

titin gene or 2) a method for determining whether a test subject has titin related *heart failure* (claims 6 and 30), before the August 1999 publication date of the Satoh reference. The exhibit has been thoroughly reviewed and seems to provide evidence that the pickwick mutation in the zebrafish could be titin (p. 004) and that "Y5T7 end is titin homologue" (p. 005). It is noted that claims 1-3, 6, 20-22 and 28-29 are specifically drawn to species of "any titin sequence" and claims 23-32 represent a genus of which only a specific species, zebrafish, is taught in the declaration. However, this disclosure is not sufficient to show that applicant was in possession of a method of determining whether a human or mammalian subject has, is at risk of developing, has an increased likelihood of developing or provides information as to the etiology of an existing heart disease or condition. The guidance provided in the MPEP states as follows:

MPEP 715.03 "Genus-Species, Practice Relative to Cases Where Predictability Is in Question"

Where generic claims have been rejected on a reference or activity which discloses a species not antedated by the affidavit or declaration, the rejection will not ordinarily be withdrawn, subject to the rules set forth below, unless the applicant is able to establish that he or she was in possession of the generic invention prior to the effective date of the reference or activity. In other words, the affidavit or declaration under 37 CFR 1.131 must show as much as the minimum disclosure required by a patent specification to furnish support for a generic claim.

In situations such as this, where predictability is in question, the MPEP states:

In cases where predictability is in question, on the other hand, a showing of prior completion of one or a few species within the disclosed genus is generally not sufficient to overcome the reference or activity. In re Shokal, 242 F.2d 771, 113 USPQ 283 (CCPA 1957). The test is whether the species completed by applicant prior to the reference date or the date of the activity provided an adequate basis for inferring that the invention has generic applicability. In re Mantell, 454 F.2d 1398, 172 USPQ 530 (CCPA 1973); In re Rainer, 390 F.2d 771, 156 USPQ 334 (CCPA 1968); In re DeFano, 392 F.2d 280, 157 USPQ 192 (CCPA 1968); In re Clarke, 356 F.2d 987, 148 USPQ 665 (CCPA 1965). In the case of a small genus such as the halogens, which consists of four species, a reduction to practice of three, or perhaps even two, species might show possession of the generic invention, while in the case of a genus comprising hundreds of species, reduction to practice of a considerably larger number of species would be necessary. In re Shokal, supra.

Accordingly, the rejection is maintained.

10. Claims 1-3, 6, and 20-32 are rejected under 35 U.S.C. 102(a) as being anticipated by Siu (Siu et al Circulation, vol 99, pages 1022-1026, March 2, 1999).

It is noted that the response dated 7/17/2007 asserts that "the claims do not specify a method that necessarily leads to an absolute, definitive diagnosis every time it is carried out. Rather, the... method can be used to identify a factor that may play a role in a disease or condition of the heart" (page 9). Upon further review of the claims, it is clear that only two steps are set forth, that is a) obtaining a nucleic acid same from a test subject, and b) analyzing the nucleic acid molecule of the sample to determine "whether" the test subject has a mutation in a [naturally occurring human] titin gene. Step b is not actually directed to detecting a mutation, but rather to analyzing to determine whether a mutation is present, which broadly reads on sequencing a gene or gene region of titin. Accordingly, the following rejection is set forth.

Siu teaches a method of obtaining a nucleic acid containing sample from a human test subject, and amplifying a naturally occurring a cardiac specific N2B exon of human titin gene sequence to determine it's sequence. With the regard to claims 1, 6, 20, 23-25, and 30, the preamble recitation merely represents an intended use of the method steps and has not been given any patentable weight. Additionally, the recitation of "wherein the presence of a mutation is an indication..." sets forth an inherent property of the mutation, rather than any actual physical process step, and has not been given any patentable weight, especially in light of the fact that the claims do not actually require detection of a mutation. Accordingly, the teachings of Siu anticipate calims 1-3, 6, and 20-32.

Claim Rejections - 35 USC § 103

11. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

12. Claims 1-3, 6, and 20, and 20-32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Genbank Accession number X90568 (March 1996) in view of Muller-Seitz (Muller-Seitz et al; Genomics, vol. 18, pages 559-561, 1993).

It is noted that the response dated 7/17/2007 asserts that "the claims do not specify a method that necessarily leads to an absolute, definitive diagnosis every time it is carried out. Rather, the... method can be used to identify a factor that may play a role in a disease or condition of the heart" (page 9). Upon further review of the claims, it is clear that only two steps are set forth, that is a) obtaining a nucleic acid same from a test subject, and b) analyzing the nucleic acid molecule of the sample to determine "whether" the test subject has a mutation in a [naturally occurring human] titin gene. Step b is not actually directed to detecting a mutation, but rather to analyzing to determine whether a mutation is present, which broadly reads on sequencing a gene or gene region of titin. With the regard to claims 1, 6, 20, 23-25, and 30, the preamble recitation merely represents an intended use of the method steps and has not been given any patentable weight. Additionally, the recitation of "wherein the presence of a mutation is an indication..." sets forth an inherent property of the mutation, rather than any actual physical process step, and has not been given any patentable weight, especially in light of the fact that the

claims do not actually require detection of a mutation. Accordingly, the following rejection is set forth.

Genbank Accession number X90568 teaches the sequence of human titin mRNA. The accession number does not specifically teach "obtaining a sample from a test subject" or analyzing the nucleic acid to determine "whether" a mutation is present. However, as noted above, the claims do not require detection of a mutation, but rather analysis to determine whether a mutation is present. Such analysis reads on sequencing, as exemplified by the dependent claims. Muller-Seitz teaches PCR amplification of a portion of the titin gene as well as sequencing the PCR fragments (page 559, col. 2, last para). Accordingly, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to sequence the titin mRNA taught the accession number, including the cardiac specific N2B exon using the PCR sequencing method taught by Muller-Seitz. The ordinary artisan would have been motivated to sequence the nucleotide sequence of the Accession number using the method taught by Muller-Seitz, as Muller-Seitz teaches the successful determination of a sequence of a titin gene using PCR amplification followed by sequencing.

Conclusion

13. No claims are allowed.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jehanne Sitton whose telephone number is (571) 272-0752. The examiner can normally be reached Monday-Thursday from 8:00 AM to 5:00 PM and on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, can be reached on (571) 272-0735. The fax phone number for this Group is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

/Jehanne Sitton/
Primary Examiner
Art Unit 1634
9/26/2007